General

Guideline Title

Recommendations for antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

Bibliographic Source(s)

Canadian Agency for Drugs and Technologies in Health (CADTH). Recommendations for antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Mar. 16 p. [49 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH therapeutic review recommendations: new oral anticoagulants for the prevention of thromboembolic events in patients with atrial fibrillation. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2012 Jun. 13 p. [18 references]

Recommendations

Major Recommendations

Recommendation 1: The Canadian Drug Expert Committee (CDEC) recommends that new oral anticoagulants should be considered for the prevention of stroke for patients with non-valvular atrial fibrillation (AF) and:

- Who have a $CHADS_2$* score ≥1; AND
- Who are unable to readily achieve adequate anticoagulation with warfarin

*C = congestive heart failure, H = hypertension, A = older than age 75 years, D = diabetes mellitus, S_2 = prior stroke or history of transient ischemic attack

Of Note

The Committee noted that because patients with a $CHADS_2$ score <2 were excluded from the ROCKET-AF trial, in which rivaroxaban was compared with warfarin, there was no evidence from this trial related to the use of rivaroxaban in patients with a $CHADS_2$ score of 1 or less.

The Committee felt that there was insufficient evidence to explicitly define "adequate anticoagulation with warfarin." The Committee felt that failure to achieve adequate anticoagulation with warfarin is sensitive to locally available resources and, as such, should be determined on a jurisdictional basis in collaboration with clinical experts. Considerations to be included in such a definition are:

- Access to testing

- Access to responsive primary care
- Time to achievement of a stable international normalized ratio (INR)
- Maintenance of a stable INR without frequent testing
- Impact of short-term perturbations (e.g., antibiotic usage)
- Patient-specific time in therapeutic range (TTR)
- Serious hypersensitivity reaction to warfarin

The Committee identified the values of safety, efficacy, and cost-effectiveness as of particular importance in making this recommendation.

Reasons for Recommendation 1

- While there were statistically significant differences between some of the new oral anticoagulants (NOACs) and warfarin for some outcomes, absolute risk differences for the NOACs versus warfarin were generally fewer than 10 events per 1,000 patients treated each year.

Recommendation 2: CDEC recommends that, if a decision is made to use a new oral anticoagulant, selection should be based on individual clinical factors.

Of Note

The Committee identified the values of safety, efficacy, and cost-effectiveness as of particular importance in recommending the use of patient-specific clinical factors in selecting a NOAC.

Reasons for Recommendation 2

- The lack of head-to-head trials and the small number of trials available to definitively assess comparative effectiveness indirectly makes evidence-based differentiation of these agents difficult.
- The relative cost-effectiveness of the NOACs is uncertain.
- The lack of long-term data for the NOACs and the assumption of persistent benefit of the NOACs beyond the durations of the individual randomized controlled trials (RCTs) available make comparison of the cost-effectiveness of the new agents unreliable.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Stroke and systemic embolism associated with non-valvular atrial fibrillation

Guideline Category

Management

Prevention

Treatment

Clinical Specialty

Cardiology

Family Practice

Geriatrics

Hematology

Internal Medicine

Pharmacology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Health Plans

Hospitals

Managed Care Organizations

Nurses

Pharmacists

Physician Assistants

Physicians

Utilization Management

Guideline Objective(s)

- To provide recommendations for the optimal management of antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation
- To help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services

Target Population

Patients with non-valvular atrial fibrillation requiring anticoagulation

Interventions and Practices Considered

1. Warfarin
2. New oral anticoagulants (dabigatran, rivaroxaban, apixaban)
3. Antiplatelets (aspirin [acetylsalicylic acid or ASA], clopidogrel)

Major Outcomes Considered

- All-cause stroke or systemic embolism (SSE)
- Major bleeding (International Society of Thrombosis and Haemostasis definition)
- All-cause mortality

- Intracranial bleeding (including intracerebral hemorrhage)
- Cardiovascular mortality
- Ischemic/uncertain SSE (including myocardial infarction [MI])
- Life-threatening bleeds
- Extracranial hemorrhage
- Minor bleeds
- Pulmonary embolism
- Transient ischemic attack
- Non-cardiovascular mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The evidence for developing recommendations was derived from the following Canadian Agency for Drugs and Technologies in Health (CADTH) clinical and economic report (see the "Availability of Companion Documents" field):

- Canadian Agency for Drugs and Technologies in Health. Antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

Research Questions

1. How do the clinical safety and efficacy of new oral anticoagulants (NOACs [apixaban, dabigatran, and rivaroxaban]) compare to warfarin, aspirin (acetylsalicylic acid [ASA]), clopidogrel, or ASA plus clopidogrel in preventing morbidity and mortality in patients with non-valvular atrial fibrillation (AF)? Are there any differences in clinical safety and efficacy depending on the dose of ASA?
2. In patients with non-valvular AF, what is the impact on the clinical safety and efficacy of NOACs on the following: $CHADS_2$* score, time spent in the therapeutic range (TTR; applicable only to warfarin), and age?
3. What is the cost-effectiveness, from a public payer's perspective, of NOACs compared with warfarin, ASA, clopidogrel, or ASA plus clopidogrel in preventing morbidity and mortality in patients with non-valvular AF based on the $CHADS_2$ score, age, and TTR?

*C = congestive heart failure, H = hypertension, A = older than age 75 years, D = diabetes mellitus, S_2 = prior stroke or history of transient ischemic attack

Systematic Review

Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with In-Process records & daily updates via Ovid; EMBASE (1974-) via Ovid; Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dabigatran, apixaban, rivaroxaban, clopidogrel, ASA, warfarin, acenocoumarol, and AF. Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs) and controlled clinical trials. Retrieval was limited to English language articles and studies published after 1988. Conference abstracts were excluded from the search results. The initial search was completed on June 7, 2012. Regular alerts have been established.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, Canadian and major

international health technology assessment agencies, clinical practice guidelines, meta-analyses and systematic reviews, as well as The Cochrane Library (2012, Issue 6) and University of York Centre for Reviews and Dissemination (CRD) databases. Google was used to search for additional web-based materials.

Details of the literature search are presented in Appendix 1 of the clinical and economic report (see the "Availability of Companion Documents" field).

Selection Criteria and Methods

Trials were included in the systematic review based on the pre-specified selection criteria that were established in the review protocol (Table 5 of the clinical and economic report [see the "Availability of Companion Documents" field]). Active and placebo-controlled RCTs were selected for inclusion if they were published in English, included at least one treatment comparison between two of the antithrombotic strategies under review, reported any of the pre-specified outcomes related to patient safety or clinical efficacy, and involved patients with AF eligible to receive anticoagulant therapy, regardless of the level of stroke risk. Trials that included patients with contraindication to anticoagulant treatment were excluded.

Two reviewers independently screened citations and selected trials relevant to the research questions on the use of antithrombotic therapy for stroke prevention in patients with AF. The reviewers screened the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria, ordered the full text of any article that appeared to meet those criteria. In cases of insufficient information, the article was ordered for more information. The two reviewers selected the final articles for inclusion based on an examination of the full-text publications. The independently chosen included and excluded studies were then compared, and disagreements were resolved through discussion until consensus was reached.

The trial selection process is presented in an appendix flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix 8 of the clinical and economic report [see the "Availability of Companion Documents" field]).

Number of Source Documents

A total of 28 articles reporting results from 12 individual randomized controlled trials (RCTs) were included in the evidence review.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction Strategy and Critical Appraisal of Individual Studies

Three reviewers independently extracted the following data for each included article, using a standardized template:

- Baseline characteristics of trial participants
- Intervention(s) evaluated, including dose, duration, and relevant co-medication
- Efficacy and safety results of the interventions for each of the pre-specified outcomes included in the protocol

All extracted data was checked for accuracy by three independent reviewers. Any disagreements in the assessment of these data were resolved through discussion until consensus was reached. Quality assessment of randomized controlled trials (RCTs) was also performed independently by two reviewers using a standardized table based on major items from the Scottish Intercollegiate Guidelines Network (SIGN 50) instrument for internal validity. Further critical appraisal was performed based on clinical input from experts.

Indirect Comparisons

Pairwise and Bayesian mixed treatment comparison (MTC) network meta-analysis (NMA) were conducted for the outcomes presented in Table 6 of the clinical and economic report (see the "Availability of Companion Documents" field). NMA for other outcomes was not conducted because data was either sparsely reported (e.g., pulmonary embolism, life-threatening bleeds, transient ischemic stroke), outcome definitions varied considerably (e.g., minor bleeds), or outcomes were redundant (all-cause stroke/systemic embolism [SE] versus ischemic stroke/SE).

WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) was used to conduct Bayesian NMA using a binomial likelihood model, which allows for the use of multi-arm trials. Pairwise fixed-effects meta-analyses were conducted for outcomes using the R meta package for the statistical software R (www.r-project.org/). Fixed and random-effects meta-analyses were conducted; the fixed-effects results are reported in the main body of the report, as the pairwise comparisons are largely comprised of single studies. Assessment of model fit for NMA comprised of assessment of deviance information criterion (DIC) and comparison of residual deviance to number of unconstrained data points. Small trials (<100 patients in each arm) with zero cells in both arms or nodes where there were no events were excluded from evidence networks because they do not contribute information or allow interpretable information. Point estimates and 95% credible intervals (CrI; Bayesian confidence interval) were modelled for odds ratios (ORs) using Markov chain Monte Carlo methods. The absolute risk difference (ARD) per 1,000 patients treated each year for each outcome was also calculated using the warfarin arm of the RE-LY trial as the baseline event rate. The RE-LY trial was selected because it was the most recent trial which contained data for both $CHADS_2$* <2 and $CHADS_2$ ≥2 and had detailed data available from the U.S. Food and Drug Administration (FDA) Public Summary Report. Vague or flat priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout the NMA. To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed. Three chains were fit in WinBUGS for each analysis, with ≥20,000 iterations, and a burn-in of ≥20,000 iterations.

*C = congestive heart failure, H = hypertension, A = older than age 75 years, D = diabetes mellitus, S2 = prior stroke or history of transient ischemic attack

Both network and pairwise meta-analysis require that studies be sufficiently similar in order to pool their results. A wide range of patient and trial characteristics were assessed to investigate the potential implications of heterogeneity across the included RCTs. The report authors identified a number of areas where there was clinical and methodological heterogeneity. The issues identified were similar to what has been reported in previous systematic reviews of drugs (e.g., differences in therapeutic range [TTR], $CHADS_2$ score). Heterogeneity was assessed by conducting NMA using the following subgroup data reported in the individual RCTs:

- TTR <66% or ≥66%
- $CHADS_2$ score <2 or ≥2
- Age <75 or ≥75 years

The methodological limitations with this approach are recognized (e.g., lack of information on similarity of patients across subgroups). Subgroup data was only available for the primary efficacy and safety outcomes in each RCT, namely all-cause stroke/SE and major bleeding; therefore, subgroup analyses were limited to these outcomes. Consequently, the ability to explore the impact of heterogeneity between studies regarding patient population and study design for other outcomes considered in the NMA was limited.

Sensitivity Analysis

Due to the exclusion of several large trials (see Appendix 10 in the clinical and economic report [see the "Availability of Companion Documents" field] for excluded studies) that contained potentially useful information that might have altered the results of the primary analysis, the report authors carried out a sensitivity analysis in which data from two studies of particular interest, namely AVERROES and ACTIVE-A, were included (instead of excluded, as in the primary analysis). The authors used data for the main efficacy and safety outcomes, specifically stroke and systemic embolism (SSE) and major bleeds. The results of this sensitivity analysis are presented in Appendix 21 of the clinical and economic report (see the "Availability of Companion Documents" field).

See the clinical and economic report (see the "Availability of Companion Documents" field) for pharmacoeconomic analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Canadian Drug Expert Committee (CDEC) is a Committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). It makes recommendations and provides advice to Canadian jurisdictions to use in making informed decisions. It is made up of experts in drug evaluation and drug therapy and public members.

The Therapeutic Review Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication's efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic Review clinical and economic reports are based on published information available up to the time that CDEC made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations is considered in the preparation of this Recommendations document.

Evidence-informed recommendations were developed by CDEC to address the following policy questions:

- In atrial fibrillation (AF) patients with a lower risk of stroke ($CHADS_2$* score <2), which antithrombotic therapy is optimal?
- In AF patients with a higher risk of stroke ($CHADS_2$ score ≥2) who are unable to achieve adequate anticoagulation with warfarin, i.e., whose time in therapeutic range (TTR) is <66%, which new oral anticoagulant (NOAC) is optimal?

*C = congestive heart failure, H = hypertension, A = older than age 75 years, D = diabetes mellitus, S_2 = prior stroke or history of transient ischemic attack

The Committee considered the evidence and its limitations primarily from a population-based perspective. The anticipated absolute benefits, harms, and cost-effectiveness of the NOACs, warfarin, and antiplatelet agents were considered to be fundamental in the development of system-level recommendations. The Committee also recognized that clinical guidelines related to the use of the NOACs have been developed based on clinical judgment and consideration of individual patient characteristics, but these guidelines failed to take into account the cost or cost-effectiveness of these treatments.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Economic Evidence

The primary objective of the economic review was to determine the cost-effectiveness of the new oral anticoagulants (NOACs [dabigatran, rivaroxaban, and apixaban]) and antiplatelet drugs (acetylsalicylic acid [ASA] with or without clopidogrel) compared with warfarin in patients with non-valvular atrial fibrillation (AF), stratified by stroke risk ($CHADS_2$* score <2 or ≥2). In addition, a more detailed stratification by $CHADS_2$ score (0, 1, ≥2 no previous stroke, ≥2 previous mild stroke, ≥2 previous major stroke) was conducted, and further stratified analysis was conducted for different age subgroups (≥60 <65, ≥65 = 70 and <75 = 70, ≥75 = 80) and based on centre specific average time in therapeutic range (TTR) (<66%, ≥66%). A variety of deterministic and probabilistic sensitivity analyses was carried out.

*C = congestive heart failure, H = hypertension, A = older than age 75 years, D = diabetes mellitus, S_2 = prior stroke or history of transient ischemic attack

The Committee considered the results of a cost-utility analysis with treatments compared in terms of the incremental cost per quality-adjusted life-year (QALY) gained over a lifetime (40 years) time horizon. The target population for the analysis was Canadians with non-valvular AF requiring anticoagulation, and the economic analysis was conducted from a third party payer perspective, specifically a Canadian Ministry of Health.

The annual costs for all treatments considered are presented in Table 1 of the original guideline document.

The economic analysis was in the form of a Markov model in which a cohort of patients with non-valvular AF received pharmacotherapy to prevent stroke. The cohort was followed from initiation of pharmacotherapy to death while simulating the incidence of death and other events associated with the patient population. Specific events modelled were transient ischemic attack, stroke or systemic embolism (SSE) (fatal, major, or minor), bleeding (fatal, intracranial hemorrhage [ICH], major non-ICH, and minor), myocardial infarction (MI), pulmonary embolism (fatal or non-fatal), and death without an event. Utility values were derived from published literature for the modelled events and assumed to decline with age.

The results of the economic analyses suggested that for patients with $CHADS_2$ <2, dabigatran 150 mg was likely the optimal treatment with an incremental cost per QALY gained versus warfarin of $20,845. For patients with $CHADS_2$ ≥2, dabigatran 150 mg and apixaban were the most

cost-effective treatments among the NOACs, and the incremental cost per QALY gained for both apixaban and dabigatran 150 mg versus warfarin was $17,795. Apixaban was likely optimal as it dominated dabigatran 150 mg in probabilistic analyses, but the difference between these two treatments is marginal.

The antiplatelet treatments were all dominated by one or more of the anticoagulants, irrespective of stroke risk ($CHADS_2$ score), age, or degree of international normalized ratio (INR) control (TTR). Therefore, compared with anticoagulants, antiplatelet therapy was never optimal in any of the subgroups analyzed. However, the paucity of data for patients with a $CHADS_2$ score = 0 suggests that these findings cannot be generalized to patients with a low risk of stroke, and must be limited to patients with a moderate or high risk of stroke ($CHADS_2$ score >0).

Relative cost-effectiveness was influenced by the following:

- Willingness-to-pay threshold (λ): The probability that dabigatran 150 mg is the most cost-effective NOAC in $CHADS_2$ <2 increases as the willingness-to-pay threshold increases. Similarly, the probability that apixaban is optimal in patients with a $CHADS_2$ score ≥2 increases as the willingness-to-pay threshold increases.
- Age: Dabigatran 150 mg was optimal in younger patients (60 or 70 years old), whereas apixaban was optimal in older patients (80 years old). None of the antiplatelet agents was optimal irrespective of age.
- Degree of INR control: In centres with poor INR control (TTR <66%), dabigatran 150 mg was optimal, while apixaban was optimal in centres with good INR control (TTR ≥66%), although there was little difference in cost-effectiveness for both therapies.

The results of the cost-effectiveness analysis were highly sensitive to the patient population under consideration, reinforcing the need for tailoring the treatment of individual patients according to individual characteristics that affect treatment outcomes, including the degree of control of warfarin therapy (assessed using TTR), age, and risk of stroke.

See the clinical and economic report (see the "Availability of Companion Documents" field) for pharmacoeconomic evidence.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations is considered in the preparation of the original guideline document.

The original guideline document was peer-reviewed by clinical experts.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The recommendations are based on clinical and economic evidence.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of antithrombotic agents for the prevention of stroke and systemic embolism (SSE) in patients with atrial fibrillation (AF)

Potential Harms

- Although the new oral anticoagulants (NOACs) are as effective at preventing stroke as warfarin, the newer drugs are more expensive and little is known about their long-term safety.
- With NOACs, patients must be regularly assessed for adherence to treatment, kidney function, drug interactions, and bleeding risk.
- With NOACs, there is no antidote or proven management strategy is bleeding occurs.

See the "Safety," "Patient Considerations," and "Other Discussion Points" sections in the original guideline document for more information.

Qualifying Statements

Qualifying Statements

- The Final Canadian Drug Expert Committee (CDEC) Therapeutic Review Recommendations or Advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.
- The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.
- The analysis in the clinical and economic report (see the "Availability of Companion Documents" field) was limited by the small number of randomized controlled trials (RCTs), and the heterogeneity of patient populations, trial designs, definitions of outcomes, and reporting of results of the included RCTs.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Canadian Agency for Drugs and Technologies in Health (CADTH). Recommendations for antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Mar. 16 p. [49 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jun (revised 2013 Mar)

Guideline Developer(s)

Canadian Agency for Drugs and Technologies in Health - Nonprofit Organization

Source(s) of Funding

Production of this report is made possible through a financial contribution from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

Guideline Committee

Canadian Drug Expert Committee (CDEC)

Composition of Group That Authored the Guideline

Committee Members: Dr. Robert Peterson (*Chair*), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani

Financial Disclosures/Conflicts of Interest

Conflicts of Interest: None

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH therapeutic review recommendations: new oral anticoagulants for the prevention of thromboembolic events in patients with atrial fibrillation. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2012 Jun. 13 p. [18 references]

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Canadian Agency for Drugs and Technologies in Health (CADTH) Web site .

Availability of Companion Documents

The following is available:

- Antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Clinical and economic report. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Mar 22. 142 p. (CADTH Therapeutic Review; vol.1, no. 1b). Electronic copies: Available in Portable Document Format (PDF) from the CADTH Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on January 16, 2013. The information was verified by the guideline developer on March 6, 2013. This summary was updated by ECRI Institute on June 17, 2013. The updated information was verified by the guideline developer on July 10, 2013.

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